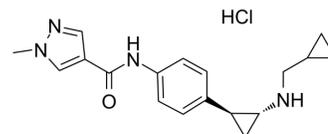


T-3775440 hydrochloride

Cat. No.:	HY-103085
CAS No.:	1422535-52-1
Molecular Formula:	C ₁₈ H ₂₃ ClN ₄ O
Molecular Weight:	346.85
Target:	Histone Demethylase
Pathway:	Epigenetics
Storage:	4°C, stored under nitrogen, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (stored under nitrogen, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 30.18 mg/mL (87.01 mM)
 H₂O : 8.33 mg/mL (24.02 mM; ultrasonic and warming and heat to 60°C)
 * "≥" means soluble, but saturation unknown.

	Solvent Concentration	Mass		
		1 mg	5 mg	10 mg
Preparing Stock Solutions	1 mM	2.8831 mL	14.4155 mL	28.8309 mL
	5 mM	0.5766 mL	2.8831 mL	5.7662 mL
	10 mM	0.2883 mL	1.4415 mL	2.8831 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
Solubility: ≥ 2.5 mg/mL (7.21 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: ≥ 2.5 mg/mL (7.21 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.5 mg/mL (7.21 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

T-3775440 (hydrochloride) is an irreversible lysine-specific histone demethylase (LSD1) inhibitor with an IC₅₀ value of 2.1 nM.

IC₅₀ & Target

IC₅₀: 2.1 nM (LSD1)^[1].

In Vitro

T-3775440 demonstrates irreversible inhibition of recombinant human LSD1, with a kinact/KI value of 1.7×10⁵ (sec⁻¹ M⁻¹). T-3775440 is highly selective for LSD1 relative to other monoamine oxidases (e.g., MAO-A and MAO-B), with an IC₅₀ value of 2.1

nM). T-3775440 blocks the proliferation of several cell lines as quickly as day 3 of treatment. Notably, the granulocyte/macrophage markers CD86 and CD11b are commonly upregulated on both TF-1a and HEL92.1.7 cells in response to T-3775440 treatment, whereas the erythroid markers CD235a and CD71 are downregulated by this treatment. In CMK11-5 cells, CD86 mRNA expression is also clearly upregulated by T-3775440 in a concentration-dependent manner, although only a modest increase in cell surface CD86 expression is observed. T-3775440 treatment disrupts the LSD1-GFI1B association in a concentration-dependent manner. T-3775440 decreases LSD1 binding but not GFI1B binding and increases the level of dimethylated H3K4 at the PI16 locus^[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

T-3775440 upregulates CD86 mRNA expression in tumor xenografts of HEL92.1.7 cells in a dose-dependent manner following the oral administration of single doses ranging from 3 to 30 mg/kg. To investigate target engagement of this compound in tumors, PI16 expression levels is tested as a direct biomarker. As expected, PI16 suppression is dramatically reversed by T-3775440 treatment. In a TF-1a (AEL) tumor xenograft model, T-3775440 exhibits significant antitumor effects, with 15-day T/C values of 15.6% and <0% at doses of 20 and 40 mg/kg, respectively. T-3775440 also exhibits potent antitumor effects in an additional AEL model of HEL 92.1.7 and an AMKL model of CMK11-5, leading to nearly complete tumor growth suppression during the dosing period. It is found that in mice, T-3775440 treatment results in a transient reduction in platelets, followed by a significant rebound; this is considered a mechanism-based adverse effect of LSD1 inhibition. On a dosing schedule comprising 5 days on/2 days off, a statistically significant difference in body weight is observed between vehicle- and T-3775440-treated tumor xenograft model mice at higher doses. However, efficacious T-3775440 doses are tolerated in all subcutaneous tumor xenograft models^[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay ^[1]

The human leukemia cell lines TF-1a, HEL92.1.7, CMK11-5 and M07e are used. All cells are grown in RPMI1640 plus 10% FBS and maintained in a humidified incubator at 37°C and 5% CO₂. To assess cell proliferation and viability in human leukemia cell lines, compounds (e.g T-3775440) are added with different concentrations (T-3775440: 0, 10, 50 nM) at 24 h after cell seeding. After the incubation period, cells are lysed with CellTiter-Glo, and luminescent signals are detected using an ARVO MX1420 microplate reader. For cell-cycle analysis, cells are fixed overnight with 70% ethanol. Fixed cells are stained with propidium iodide and analyzed on a FACSCalibur or FACSVerse flow cytometer^[1].

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Animal Administration ^[1]

Mice^[1]

Female C.B17/Icr-scid/scid Jcl mice are used and maintained under specific pathogen-free conditions. AML cells (2×10⁶ cells) in Matrigel are inoculated subcutaneously into the left flanks of 6- to 7-week-old mice (day 0). Mice are randomized when the mean tumor volume reached approximately 150 to 350 mm³. Subsequently, mice are administered with vehicle or T-3775440 single doses ranging from 3 to 30 mg/kg once daily on 5 days on/2 days off schedule for 2 weeks. Twice weekly, tumors are measured with vernier calipers, and tumor volumes are calculated^[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2019 Aug 12;36(2):123-138.e10.
- Elife. 2023 Jan 25;12:e84618.

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REFERENCES

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